Insulin Breast Cancer Connection: Confirmatory Data Set the Stage for Better Care

Andrea DeCensi, Galliera Hospital, Genoa; European Institute of Oncology, Milan, Italy
Alessandra Gennari, Galliera Hospital, Genoa, Italy


A growing body of evidence indicates a strong association between type 2 diabetes and cancer. These two common diseases, increasing in incidence as a consequence of Western lifestyle, frequently occur in the same patient. The biologic nature of this association, however, is not completely clear. Epidemiologic data suggest that patients with diabetes have a higher risk of developing several types of cancer, including liver, pancreatic, colorectal, gynecologic, and breast cancer. Cancer prognosis has also been suggested to be adversely affected by diabetes. In recent years, extensive research has attempted to evaluate and clarify the possible links between type 2 diabetes and breast cancer. In particular, the role of insulin in breast cancer etiology and prognosis has received growing attention.2

The association between insulin and cancer is biologically plausible: hyperinsulinemia induces proliferative tissue abnormalities because of the strong anabolic effect of insulin, which results in stimulated DNA synthesis and cell proliferation. This effect may also be explained by the cross-activation of the insulin-like growth factor (IGF) receptor family.3 IGFs are endocrine mediators of growth hormone and also act in a paracrine and autocrine fashion to regulate cell growth, differentiation, apoptosis, and transformation in different tissues, including breast tissue. The pathways downstream of the insulin/IGF system are well defined: insulin-like growth factor-I (IGF-I) and insulin activate the tyrosine kinase growth receptor pathway, that is, insulin, IGF-I, and hybrid IGF-II/insulin receptors, all of which are frequently overexpressed in breast cancer cells. Activation of these receptors results in upregulation of the insulin receptor substrate 2, which leads to downstream activation of the mitogen-activated protein kinase and phosphatidylinositol 3-kinase-Akt pathways.5

In this issue of Journal of Clinical Oncology, four articles6-9 shed additional light on the prognosis of breast cancer in women with diabetes or insulin resistance. All of the studies provide additional proof of an unfavorable breast cancer prognosis in patients with either overt or undiagnosed type 2 diabetes or patients with different forms of glucose intolerance as defined by high C-peptide, high homeostasis model assessment (HOMA) index (ie, the ratio of fasting blood glucose to insulin), and low adiponectin levels. In the first article, a meta-analysis by Peairs et al9 the investigators were able to detect, using standard meta-analytic procedures, a 49% increased risk of death as a result of nonspecific breast cancer in women with breast cancer and diabetes compared with women with breast cancer who did not have diabetes. Adverse prognostic features, such as delayed diagnosis and suboptimal treatments, were more likely to occur in the population with diabetes. Breast cancer-specific mortality analysis yielded inconsistent results, possibly because of the small number of available studies with specific mortality data (two out of six) and the short follow-up (one study had a follow-up of only 1 year). This meta-analysis does not come without some limitations; the most important limitation is that it is based on published data. Although it is unlikely that mortality results would differ in an analysis conducted on individual patient data, quality control and analyses of the original records were not possible, and the only feasible subgroup analyses were those for which information was available in the original reports. Despite these constraints, this pragmatic analysis provides quantitative evidence of a significantly increased risk of death in patients with breast cancer who also have a clinical diagnosis of type 2 diabetes. Moreover, given the indirect method of diabetes ascertainment, it is possible the risk of death was underestimated. Indeed, undiagnosed or delayed-diagnosed diabetes in patients who are asymptomatic has been reported to occur in approximately 30% of patients with breast cancer.10

The clinical importance and prognostic relevance of undiagnosed and unreported type 2 diabetes in patients with breast cancer is particularly evident in the article by Erikson et al.7 In this study, archived baseline blood samples from the Women’s Healthy Eating and Living study, a dietary intervention trial, were retrieved to measure baseline hemoglobin A1c to evaluate the prognostic effect of chronic hyperglycemia among 3003 survivors of early breast cancer who were observed for a median of 7.3 years for additional breast cancer events and 10.3 years for all-cause mortality. In this retrospective analysis, 6% of the patients had chronic hyperglycemia as defined by A1c levels of 6.5% or greater. A1c level was significantly associated with an increased risk of all-cause mortality (hazard ratio [HR], 2.35; 95% CI, 1.56 to 3.54, for A1c > 7.0% v < 6.5%) after adjustment for stage, grade, age, ethnicity, education, and physical activity. When adjusting for the same factors, the breast cancer–specific event rate (disease-free survival) did not differ significantly by A1c levels. However, women with A1c levels of greater than 7.0% had a clinically meaningful, albeit not significant, 26% increased risk of breast cancer recurrence. Given the retrospective nature of the study and the inconsistent association between hyperglycemia and breast cancer recurrence found in some studies,11 these results should be regarded as
hypothesis-generating findings that require additional confirmation before A1c screening is introduced into routine clinical practice. Moreover, the cost effectiveness of A1c screening may be challenged by the low prevalence (only 6%) of altered A1c levels in the study population.

Two additional works derived from the Health, Eating, Activity, and Lifestyle Study\textsuperscript{8,9} analyzed the prognostic significance of markers of glucose intolerance and obesity on all-cause and breast cancer–related death among approximately 600 women with stage I to IIIa breast cancer, most of whom did not have diabetes, who were observed for a median of approximately 6 years. In the study by Irwin et al.,\textsuperscript{8} a 1 ng/mL increase in serum C-peptide level, a reliable and stable marker of insulin secretion, was associated with a 31% increased risk of any death (HR, 1.31; 95% CI, 1.06 to 1.63) and a 35% increased risk of death as a result of breast cancer (HR, 1.35; 95% CI, 1.02 to 1.87). Associations were stronger for women with a body mass index of less than 25 kg/m\textsuperscript{2}, women with higher-stage disease, and those with estrogen receptor–positive disease. The results are in line with those previously reported by Goodwin et al.,\textsuperscript{12} who showed a three-fold estrogen receptor–positive disease. The results are in line with those of all four works\textsuperscript{6-9} omarkers and mortality were not always consistent and were of borderline significance. Nevertheless, the results of all four works\textsuperscript{6-9} published in this issue of JCO harbor important clinical implications, given the growing body of evidence that shows that treatment of diabetes and insulin resistance with dietary interventions, increased physical activity, and insulin-lowering drugs, such as metformin, may improve prognosis and responsiveness to anticancer treatments in patients with diabetes and breast cancer.\textsuperscript{17}

In particular, the renewed interest in metformin in cancer prevention and treatment is the consequence of the recent convergence of several areas of research. Exciting preclinical studies have demonstrated that metformin can inhibit the growth of cancer cells in vitro and in vivo.\textsuperscript{19} Moreover, recent data indicate that the abnormally high proliferative activity of premalignant and malignant cells requires high levels of nutrients to meet the increased demands for energy consumption and protein biosynthesis.\textsuperscript{19} Aberrations of genes involved in the metabolic pathways, such as the AMP-activated protein kinase/LKB1 pathway, thus represent an emerging hallmark of carcinogenesis that is increasingly recognized as a plausible preventive and therapeutic target.\textsuperscript{20}

Inexpensive and well tolerated, metformin is a widely prescribed antidiabetic drug for the treatment of hyperglycemia, hyperinsulinemia, and polycystic ovarian syndrome.\textsuperscript{21} Preliminary data also show an increase in adiponectin levels with metformin treatment.\textsuperscript{22} Metformin effects on cancer outcome have been retrospectively evaluated in population studies that show a lower cancer-specific mortality rate in patients with diabetes who were treated with metformin compared with other treatments,\textsuperscript{23} as well as an improved responsiveness to preoperative chemotherapy in patients with breast cancer and diabetes compared with patients with breast cancer who do not have diabetes.\textsuperscript{24} A phase III adjuvant trial has recently been initiated (Metformin Hydrochloride in Treating Patients With Early-Stage Breast Cancer [NCICMA.32]) to assess the efficacy of adding metformin to standard adjuvant treatment to reduce breast cancer recurrence in more than 3,500 women with stage I and II breast cancer.\textsuperscript{17} Metformin has also been associated with decreased cancer risk in observational studies in patients with diabetes,\textsuperscript{25} with an overall, statistically significant 31% decrease in global cancer risk and a nonsignificant 30% decrease (summarized risk ratio, 0.70; 95% CI, 0.28 to 1.77) in breast cancer incidence compared with other antidiabetic treatments (Table 1).

Whereas the routine use of metformin in any patient with breast cancer for the purpose of reducing breast cancer recurrence is still premature and requires convincing evidence from dedicated clinical trials, a few simple procedures are ready to be introduced into clinical practice. First, the measurement of waist circumference should be

### Table 1. Observational Studies That Assessed Metformin Use and Breast Cancer Risk in Patients With Diabetes

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Design</th>
<th>Population</th>
<th>Risk Estimates</th>
<th>95% CI</th>
<th>Adjusting Variables*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Libby et al., 2009</td>
<td>Scotland, United Kingdom</td>
<td>Population-based, historical cohort study</td>
<td>N = 8,170</td>
<td>0.6</td>
<td>0.32 to 1.10†</td>
<td>Smoking, BMI, HbA1c, material deprivation, other drug use (sulfonylureas or insulin)</td>
</tr>
<tr>
<td>Currie et al., 2009</td>
<td>United Kingdom</td>
<td>General practices, retrospective cohort study</td>
<td>N = 7,897</td>
<td>1.02</td>
<td>0.71 to 1.45†</td>
<td>Smoking, comorbidity, HbA1c, diabetes duration, weight</td>
</tr>
<tr>
<td>Bodmer et al., 2010</td>
<td>United Kingdom</td>
<td>Nested case-control study</td>
<td>17 cases, 120 controls</td>
<td>0.44</td>
<td>0.24 to 0.82†</td>
<td>General practice and calendar time, other use of prandial glucose regulators, acarbose, estrogen, smoking, BMI, diabetes duration, and HbA1c</td>
</tr>
</tbody>
</table>

Summary risk ratio | 0.70 | 0.28 to 1.77

NOTE: Data are modified from study by DeCensi et al.\textsuperscript{26} Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c.

*Adjusting variables listed do not include age or sex.
†As compared with nonmetformin users.
‡As compared with sulfonylureas monotherapy.
mandatory in all patients with breast cancer to detect visceral obesity (males ≥ 94 cm; females ≥ 80 cm). Visceral obesity was the main feature of the metabolic syndrome that is associated with the chronic hyperglycemia, hyperinsulinemia, and type 2 diabetes studied in the four articles discussed. The metabolic syndrome also includes any two of the following four features: a fasting plasma glucose level of 100 mg/dL or greater, raised blood pressure (systolic: ≥ 130 mmHg, or diastolic: ≥ 85 mmHg), a high-density lipoprotein cholesterol level of less than 40 mg/dL in men and less than 50 mg/dL in women, and triglyceride levels of 150 mg/dL or greater. Patients with these characteristics are at higher risk for cardiovascular disease and impaired glucose intolerance or diabetes is increasingly pointing to the accumulating evidence of common pathways linking breast cancer to diabetes. In the era of treatment selectivity and molecular-targeted anticancer drugs, the influence of insulin resistance on breast cancer progression. In the future research. Cancer Epidemiol Biomarkers Prev 18:11-27, 2009

In summary, the findings provided in this issue of JCO highlight the influence of insulin resistance on breast cancer progression. In the era of treatment selectivity and molecular-targeted anticancer drugs, the accumulating evidence of common pathways linking breast cancer and impaired glucose intolerance or diabetes is increasingly pointing the way forward. The time has come to overcome the conventional tunnel vision that results in two diseases being treated by separate clinicians, and to move towards a comprehensive approach that ideally integrates oncologists, internists, nutritionists, and other health care professionals in an attempt to improve breast cancer prognosis in a significant proportion of patients.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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